CHRONOPHARMACOLOGY

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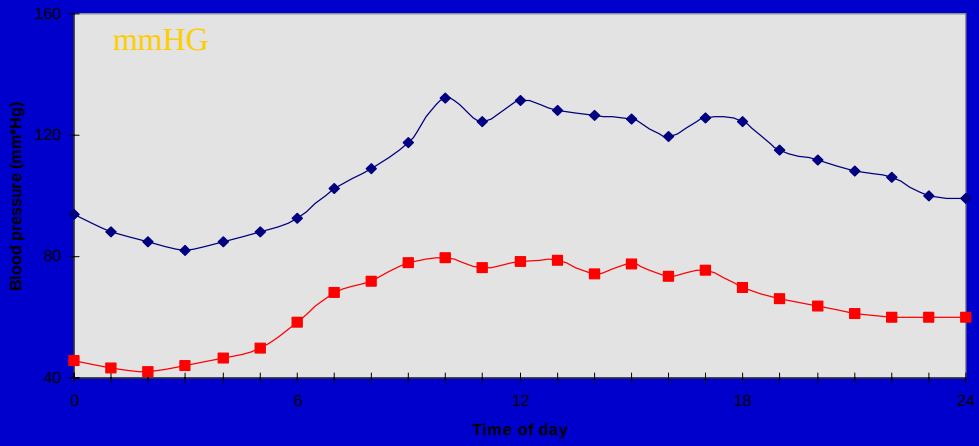
PROCESSES RELATED TO HOMEOSTASIS

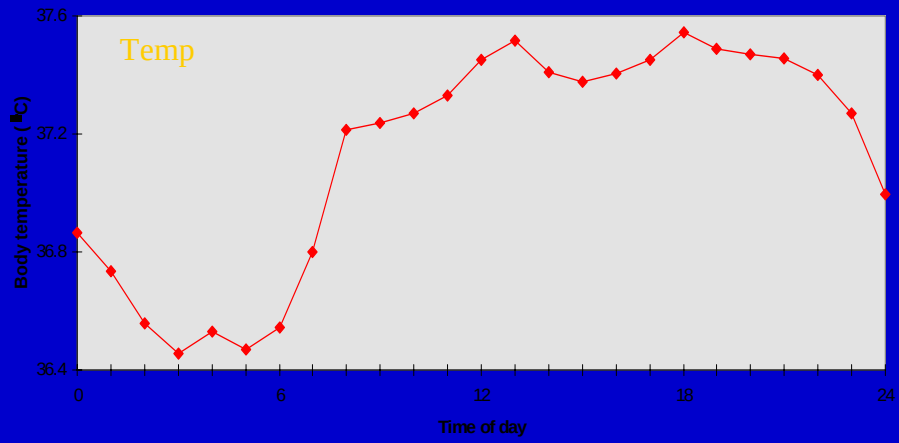
- BIOLOGICAL RHYTHMS
  - CIRCADIAN RHYTHM
  - CLINICAL APPLICATION
    - JET LAG
    - ASTHMA/MYOCARDIAL INFARCTION
    - PHARMACOLOGY
      - CHRONOPHARMACOLOGY
      - CHRONOTOXICITY

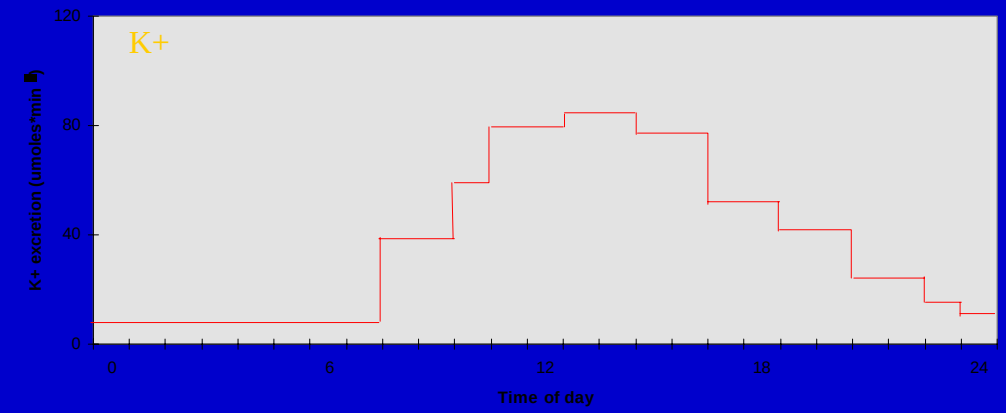
BIOLOGICAL RHYTHMS IN HUMANS

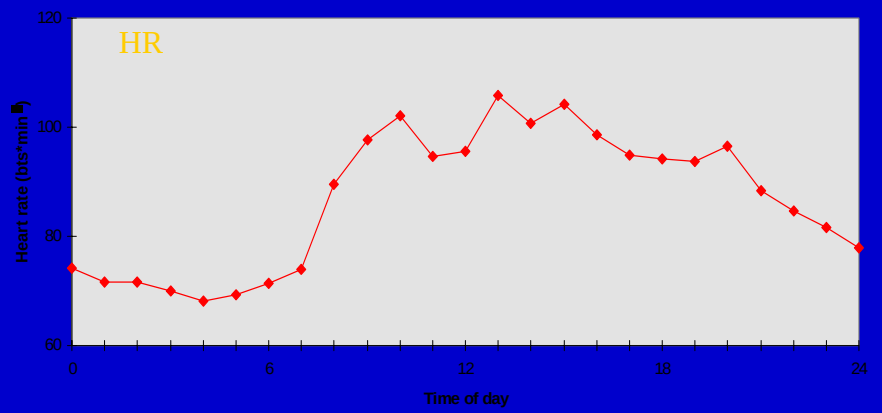
- 100 different, measurable parameters in human body – exhibit rhythmic variability within 24 hours
- BIOLOGICAL RHYTHM – an innately determined rhythmic biological process or function.
- A biological rhythm is a self-sustaining oscillation with the duration of time between successive repetitions (ie, the period) being rather nonvarying under normal conditions.

DAILY CHANGES









CIRCADIAN RHYTHMS

Circadian rhythms are particularly important in medicine.

A circadian clock in the brain coordinates daily physiological cycles

- sleep/wake
- temperature
- digestion
- hormones

Circadian (*circa*, about; *dies*, day, or about 24 hour)

- Physiological day is about 25 hours
- Clock is reset daily by the environment
  - day/night
  - social schedules

BIOLOGICAL RHYTHMS IN HUMANS

- The inherited period of the circadian clock of most persons is slightly longer than 24 hours.
- Environmental time cues termed **synchronizers**, the most important being one's *daily activity in light* and *sleep in darkness*, set the circadian clock to 24 hours on a day-to-day basis.

BIORHYTHMS

- External cues which reset the circadian clock = **ZEITGEBERS = synchronizers**

- LD, **light-darkness**
- EF, eating-fasting
- SI, **social contact-isolation**
- NQ, **noise-quiet**

BIORHYTHMS

- Endogenous nature of circadian biologic rhythms.
- Lack of external synchronizers leads to **free-running rhythms**.
- The period of free-running rhythms is longer or shorter than 24 hours and is characteristic for each species.
- Our internal clocks are GENETICALLY DETERMINED.

- An internal biological clock, located, in mammals, in the **suprachiasmatic nucleus** of the hypothalamus (**SCN**), delivering its message of time throughout the body.
- It is responsible for circadian rhythms and annual / seasonal rhythms.
- The SCN uses its connections with the autonomic nervous system for spreading its time-of-day message, either by setting the sensitivity of endocrine glands (i.e., thyroid, adrenal, ovary) or by directly controlling an endocrine output of **pineal gland** (i.e., melatonin synthesis).

Primary Mammalian Circadian Pacemaker

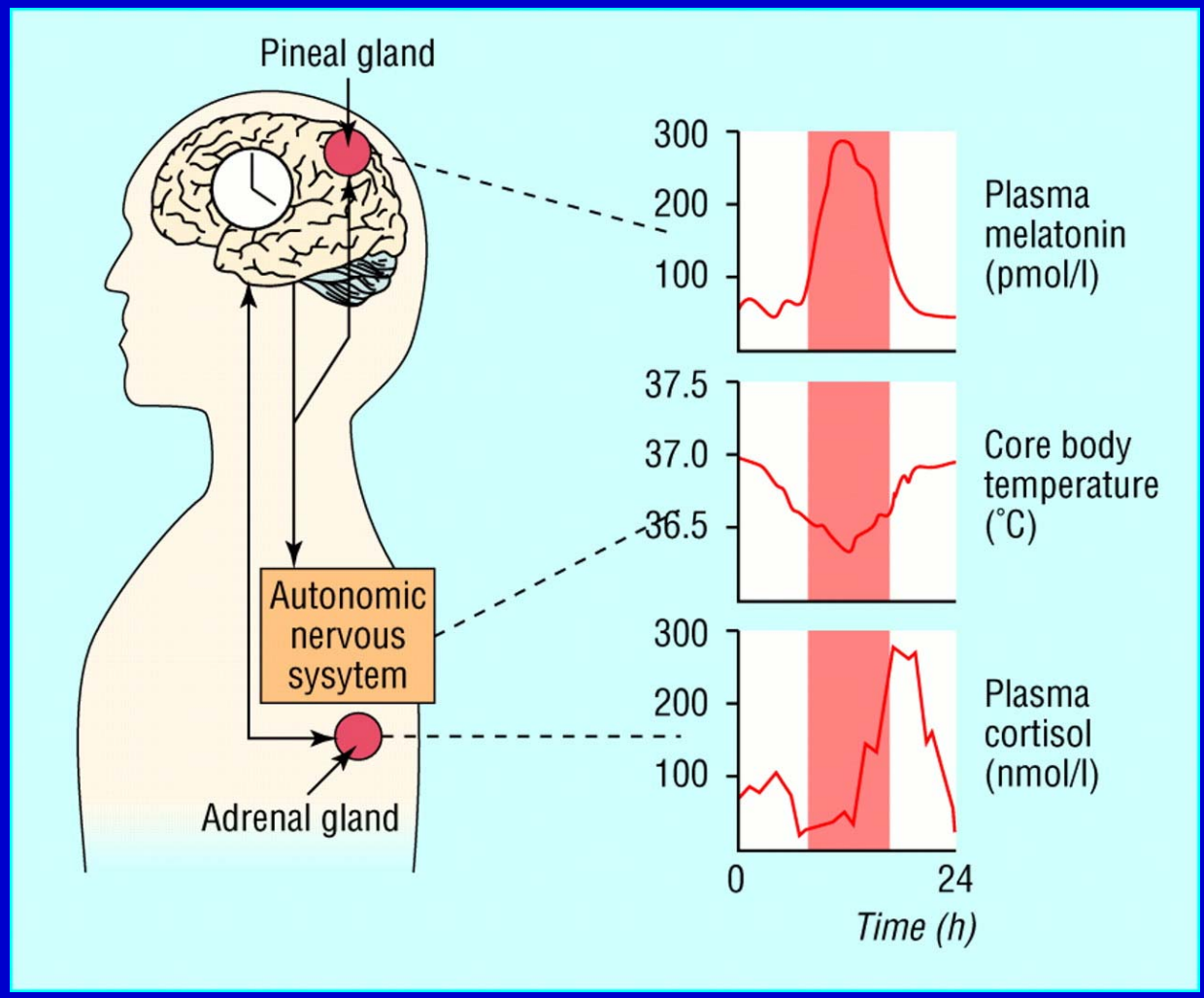
Supra-Chiasmatic Nucleus

Synchronizes with local Day/Night by Sensing
light dark not via Rods and Cones

not via cryptochromes

Photoreceptor appears to be Melanopsin, within inner layers of retina (not image formation)

Rollag, et al. (00, J. Neuroscience)


Pineal gland
Autonomic nervous sysytem
Adrenal gland
300
200
100
Plasma melatonin (pmol/l)
37.5
37.0
36.5
Core body temperature (˚C)
300
200
100
Plasma cortisol (nmol/l)
0
24
Time (h)

BIOLOGICAL RHYTHMS IN HUMANS

- The science dealing with the phenomenon of rhythmicity in living organisms is called CHRONOBIOLOGY.
- In medicine, 3 disciplines take into account the influence of time:
  - CHRONOPHYSIOLOGY
  - **CHRONOPATHOLOGY**
  - **CHRONOPHARMACOLOGY**

The branch of **chronobiology** dealing with the pharmacologic aspects is termed CHRONOPHARMACOLOGY.

Chronopharmacology is the investigative science concerned with the biological rhythm dependencies of medications.

It may be subdivided into **chronotherapy**, **chronopharmacokinetics** and **chronotoxicity**.

New technology makes possible CHRONOTHERAPY (= CHRONOTHERAPEUTICS), that is, increase of the efficiency and safety of medications by proportioning their concentrations during the 24 hours in synchrony with biological rhythm determinants of disease.

- The pharmacotherapy of medical conditions generally entails the scheduling of prescription medications that possess drug-delivery technologies that achieve the **homeostatic** goal of CONSTANCYof blood and tissue DRUG CONCENTRATION. It is assumed that the need for medication by patients is nonvarying throughout the 24 hours and that constancy of drug level translates into constancy in drug effect.
- Knowledge of day-night and other predictable-in-time variation in the symptom intensity and risk of acute exacerbations of disease coupled with evidence of circadian rhythms in the kinetics, effects, and safety of medications constitutes the rationale for a new pharmacologic approach to treatment-CHRONOTHERAPEUTICS.

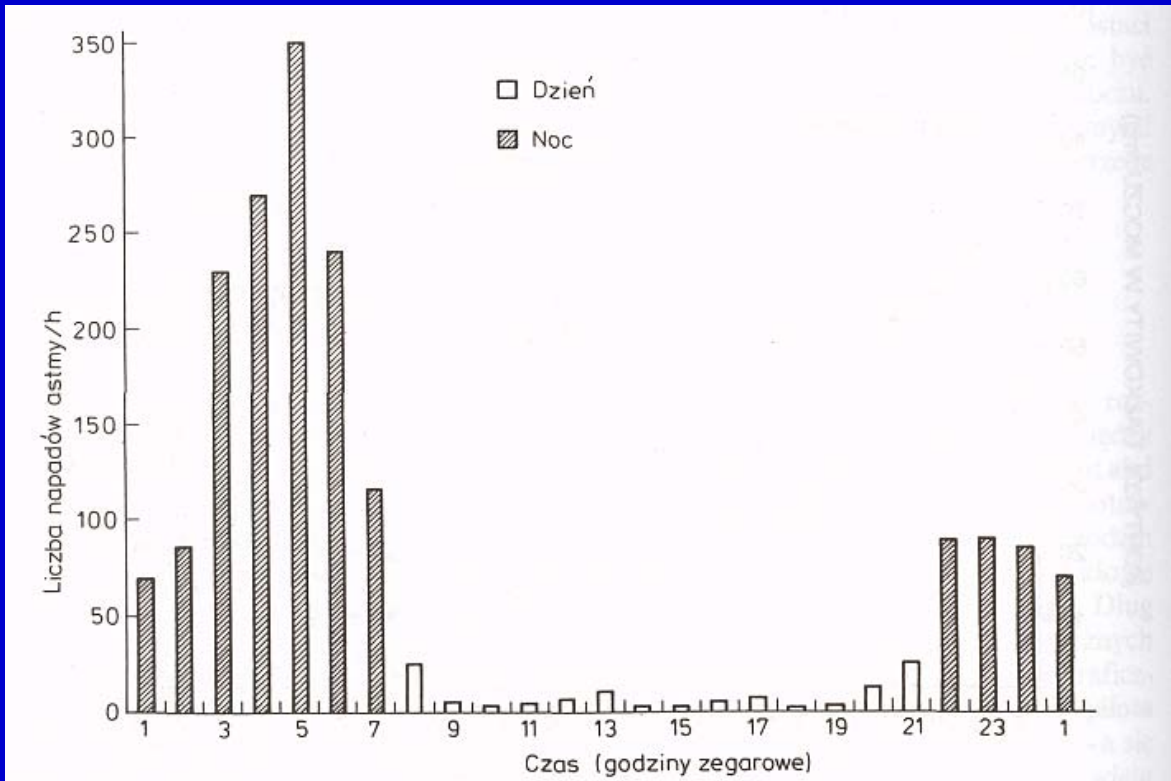
- A **chronotherapeutic approach** is indicated when the risk of severe medical events or the intensity of diseases and their symptoms is known to vary predictably during the 24 hours and/or other time periods.
- Large-scale clinical trials have shown that the efficiency and safety of certain conventional (so-called homeostatically formulated) medications can be improved by dosing them with reference to the circadian time structure.

This was first demonstrated during the 1960s; once-daily morning as opposed to multiple-daily dosing of **methylprednisolone** tablets reduces the risk of hypothalamic-pituitary-adrenal suppression and improves the treatment of severe inflammatory conditions. Other examples:

- the once-daily supper-time dosing schedule of conventional **H2-receptor antagonists** to avert the nocturnal increase in gastric acid secretion in the treatment of peptic ulcer disease and the
- evening timing of **HMG-CoA reductase antagonists**, taking into account the evening increase of cholesterol synthesis in the liver.

CHRONOTHERAPEUTICS

- Asthma. The risk of asthmatic attack is almost 70 times higher in patients at 04:00-05:00 in the morning, compared with the afternoon.



Ryc. 19.11.

Częstość występowania napadów astmy oskrzelowej w ciągu doby (modyfikacja własna za Dethlefsen i Repges).

CHRONOPATOLOGIA & CHRONOTERAPIA

Causes of this phenomenon:

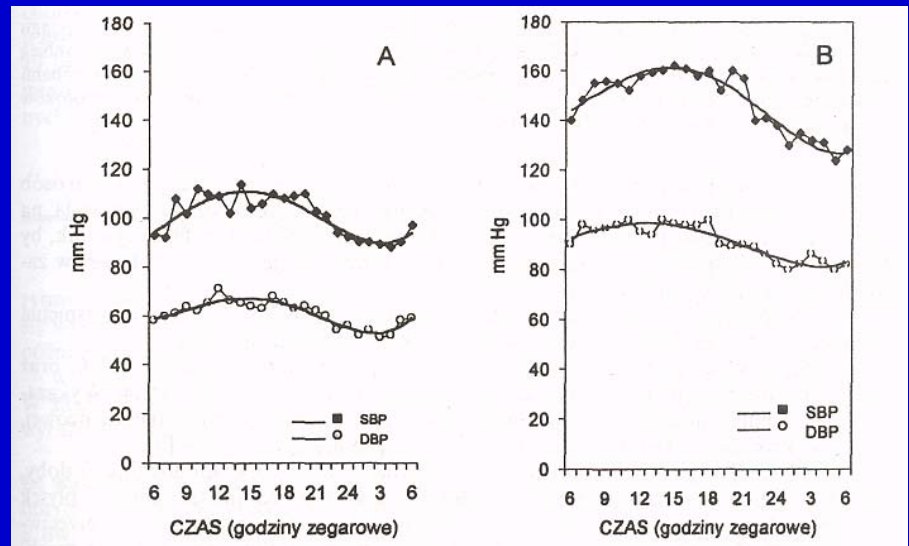
- Exogenous factors (allergen exposure, temperature changes during the day, night break in bronchodilator use, supine position during sleep, gastroesophageal reflux)
- **Endogenous factors**. Small bronchi diameter significantly increases during the day and decreases at night (adrenergic blockade of ß-receptors, dominance of alpha-adrenergic pathways, cholinergic dominance, smallest concentrations of cortisol, smallest concentrations of Ig E and highest concentration of histamine around 04:00.

CHRONOTHERAPEUTICS

- New technology makes possible the temporal modulation of drug levels in relation to patient requirements. During the 1980s, the Purdue Frederick Company in the United States and the Byk Gulden Company in Germany each began marketing a **theophylline** chronotherapy for nocturnal asthma. Evening administration of these special dosage forms results in elevated theophylline concentration during the nighttime when the likelihood of asthma is greatest and lowest drug level during the day when the risk of disease is least.

CHRONOTHERAPEUTICS

- Twenty-four-hour patterns in **cardiovascular diseases** have been documented by numerous investigators.
- Circadian rhythms of BLOOD PRESSURE in healthy subjects – nocturnal lowering of BP and a rapid elevation between 05:00-09:00 o'clock in the morning.

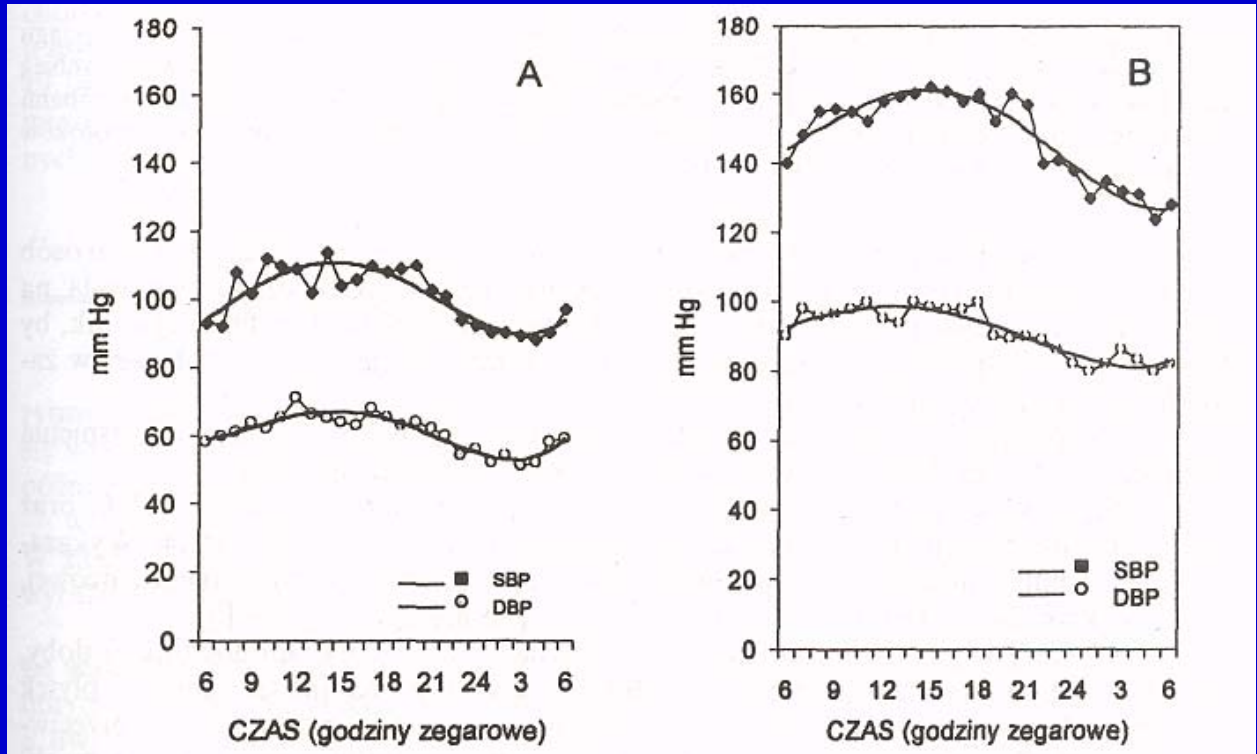


Ryc. 19.12.

Profile dobowe ciśnienia tętniczego krwi u osób z normotensją (A) i nadciśnieniem tętniczym (B)

CHRONOTHERAPEUTICS

- Hypertensive patients usually present with similar patterns but the mean arterial pressure is higher.



Ryc. 19.12.

Profile dobowe ciśnienia tętniczego krwi u osób z normotensją (A) i nadciśnieniem tętniczym (B)

CHRONOTHERAPEUTICS

- The morning RISE in BP is associated with numerous complications of hypertension.
- The lack of **nocturnal lowering** is often associated with malignant hypertension and poor prognosis.
- It is smaller in males and decreases with age.
- **Nondippers**:

- about 10% of healthy individuals
- about 20% of hypertensives (primary htn)
- > 30% hypertensives (secondary hypertension)

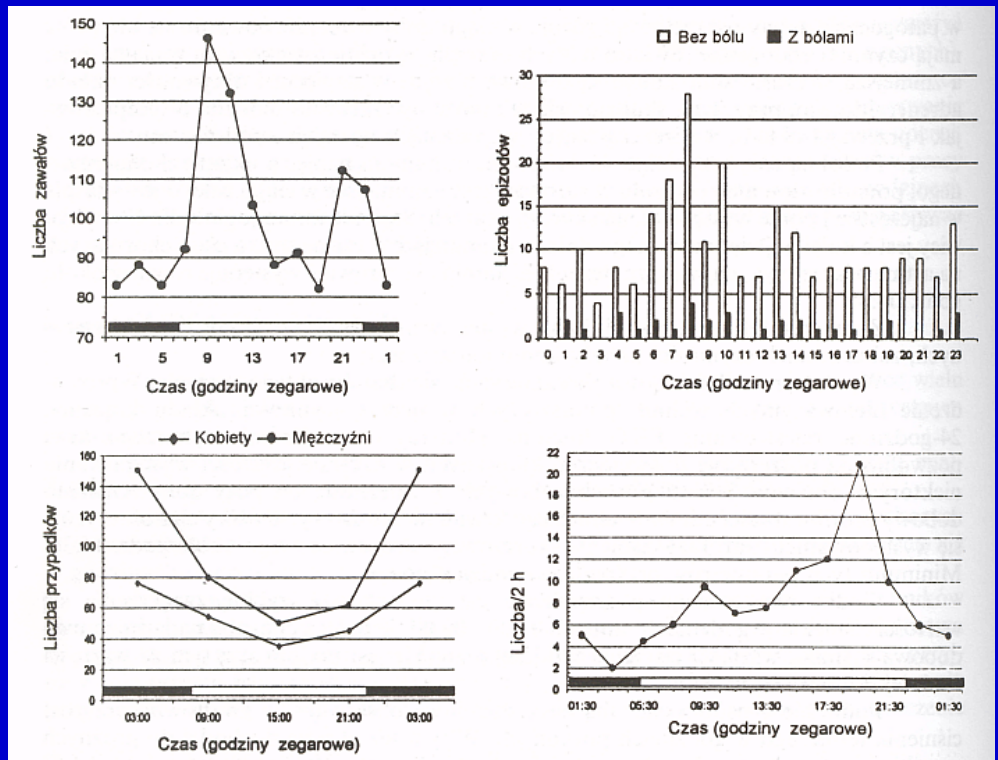
CHRONOTHERAPEUTICS

- Bedtime dosing of long-acting antihypertensive agents helps restore BP control in the morning and bring back normal circadian rhythm of BP (nondipper-dipper).

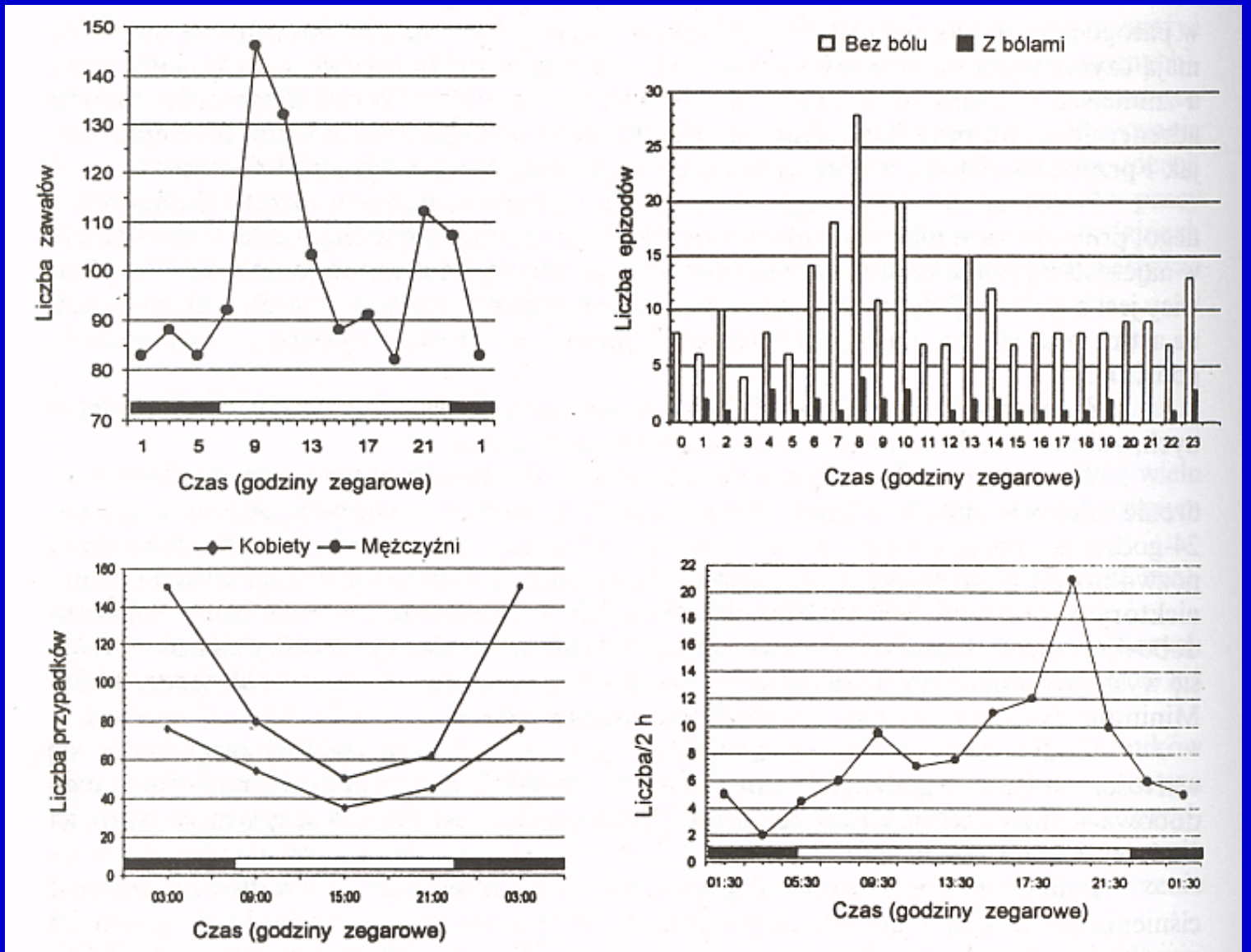
CHRONOTHERAPEUTICS

- In diurnally active patients, **angina**, acute myocardial infarction (AMI), sudden cardiac death, and ischemic and hemorrhagic stroke each is several-fold more frequent in occurrence during the initial 3 to 5 hours of morning activity (about 10 a.m.) than at any other time of the day or night.

- In contrast, episodes of vasospasm in Prinzmetal angina are most common during the sleep span, as are the symptoms of patients with congestive heart failure.

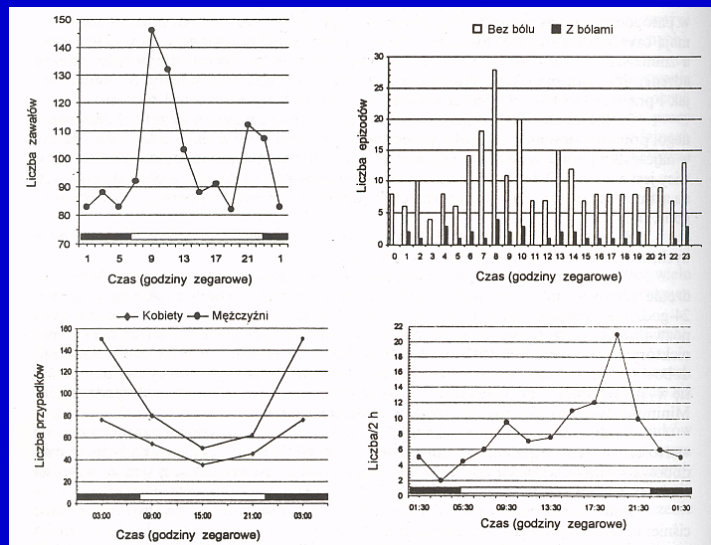


- Upper-left side — number of infarctions during 24 hrs, uper-right — ST-segment lowering in ECG in patients with CAD; lower-left side — incidence of cerebrovascular incidents (rhomb – women, circles - men), lower-right side — incidence of hemorrhagic strokes.



CHRONOTHERAPEUTICS

- Increased blood coagulation in the morning – decreased efficacy of anticoagulants and fibrinolytic agents.



- Increased incidence of CAD and strokes is connected with:

  * incr. sympathetic tone,

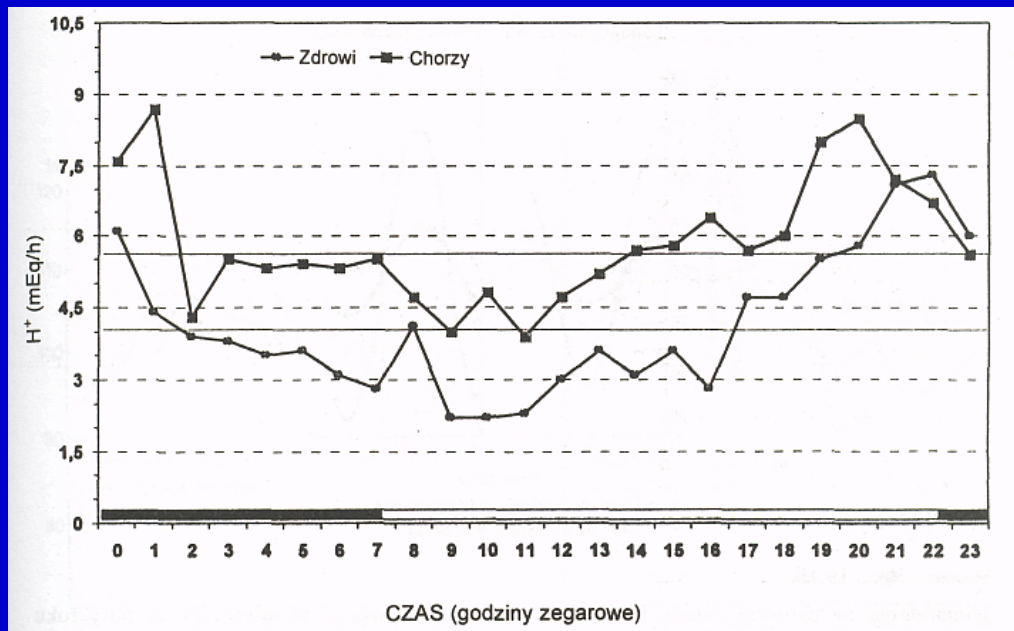
  * the rapid increase in BP, HR, and myocardial oxygen demand (the rapid elevation in BP at the start of the activity span constitutes a shearing stress of sufficient magnitude to cause rupture of unstable coronary plaques with thrombosis and AMI as sequelae),

  * incr. blood coagulation, and coronary vessel inflammation and reactivity

- The results of selected investigations that addressed circadian rhythms in the effects of antihypertensive, antiarrhythmic, and anticoagulant therapies.
- In general, the [beta]-adrenoceptor and calcium channel antagonists of propranolol, oxprenolol, atenolol, pindolol, nifedipine, and verapamil exert stronger effects on HR and BP during the day than nighttime. Enalapril produces a greater (and more rapid onset of) effect on daytime BP when dosed once per day in the morning, whereas it has greater effect on nighttime BP when dosed once per day in the evening. Once per day at evening compared with morning ingestion of isradipine better normalizes the disturbed circadian rhythm of BP in non-dialysis chronic renal failure patients. The effects of ramipril and quinapril on BP are also dependent on administration time; a morning once-per-day dosing schedule reduces sleep-time BP in a moderate amount, whereas an evening one reduces it excessively, especially with quinapril. The dosing-time dependencies of diltiazem on BP are different; the morning once-daily ingestion schedule exerts strong effect on nighttime BP, whereas the evening one produces a strong effect on it during the morning and afternoon.

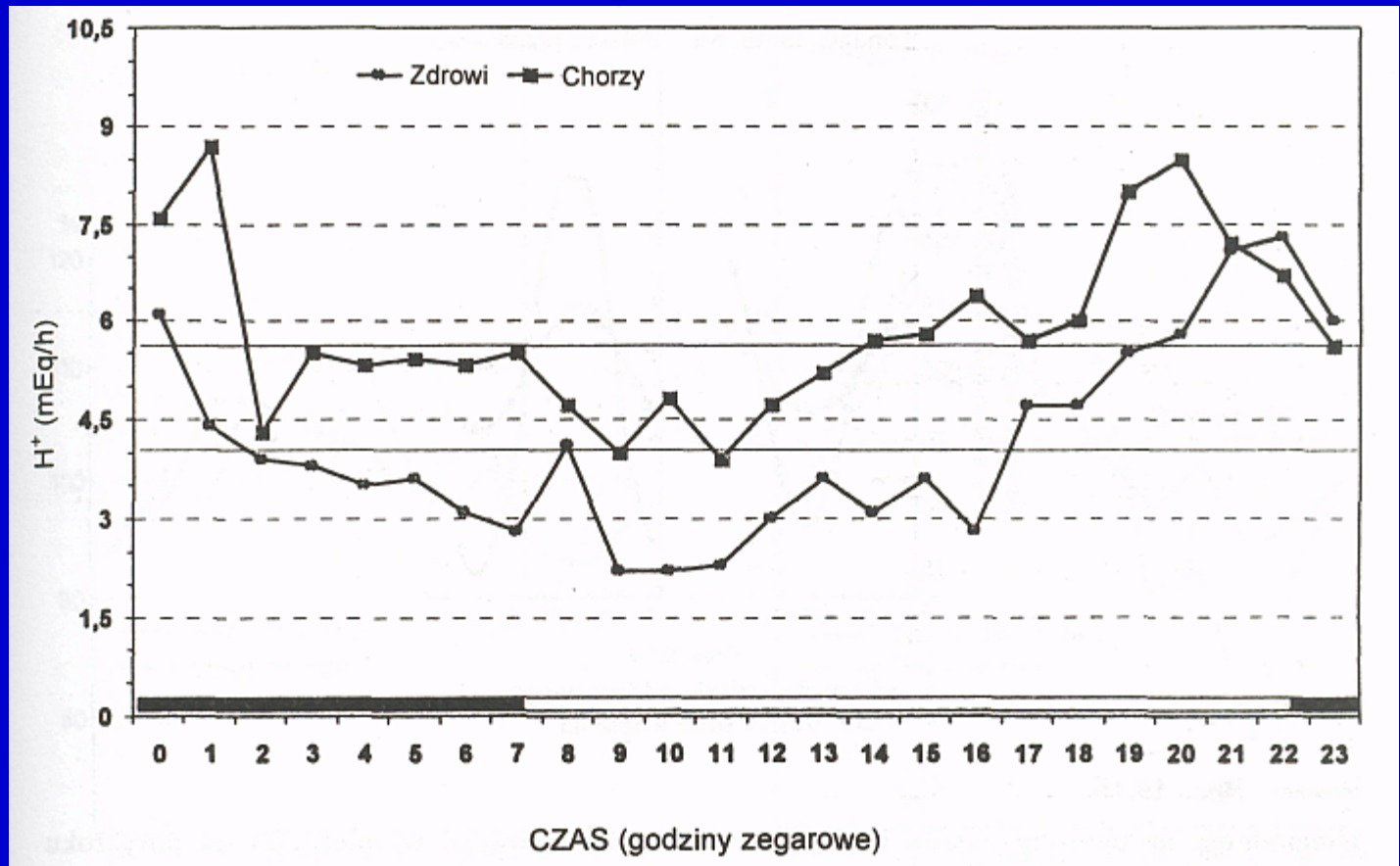
CHRONOPATOLOGIA & CHRONOTERAPIA

- Pathogenesis of stomach ulcers is associated with Helicobacter pylori and H+ secretion by the stomach.
- Acidity (H+) reaches its peak in the evening in both the healthy and persons affected by gastric ulcers.



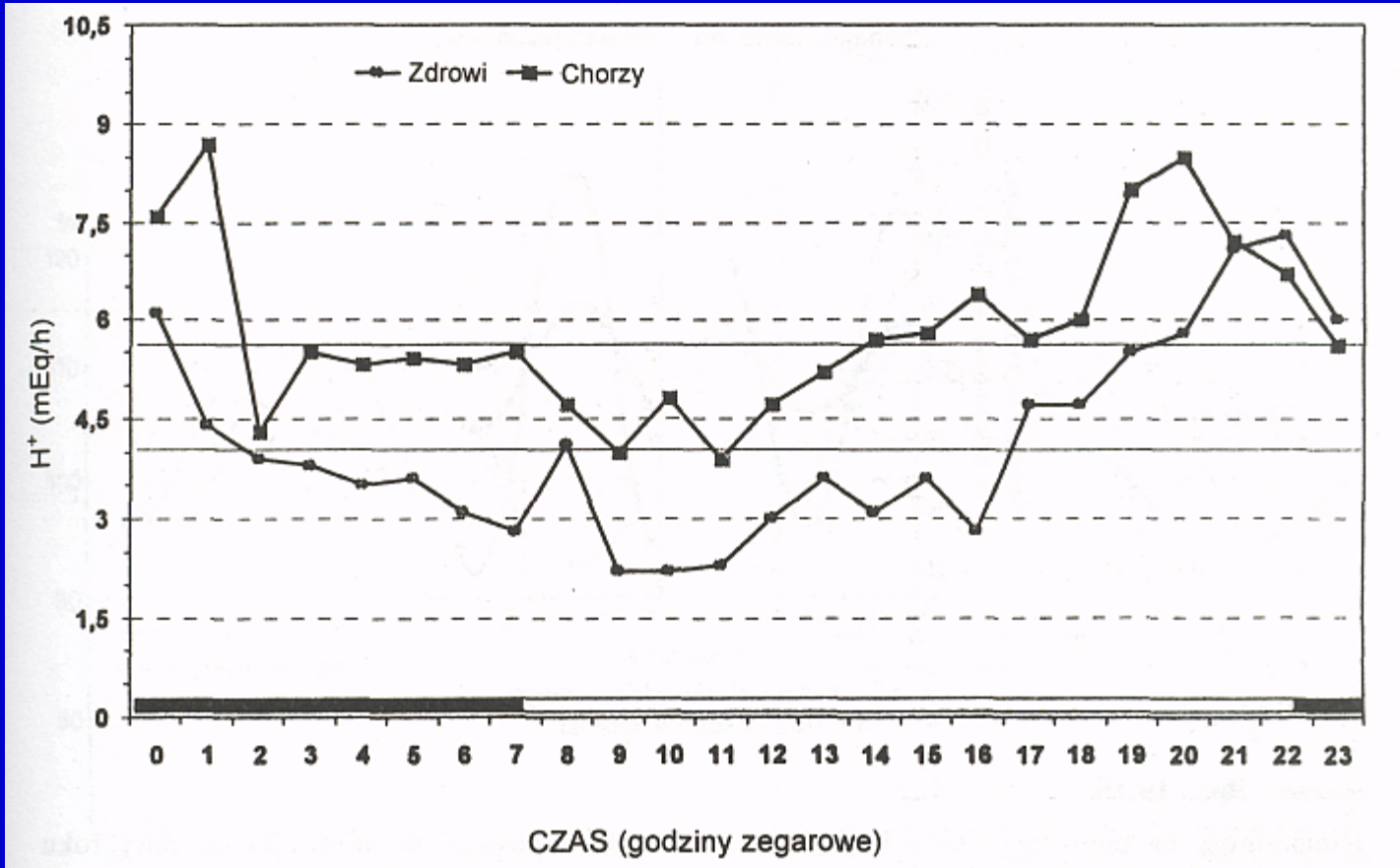
CHRONOTHERAPEUTICS

- The difference between the sick and the healthy lies in the daily average, for healthy equalling 4,12 + 0,40 mEq H+/h, for the sick 5,76 ±0,98 mEq H+/h.



CHRONOTHERAPEUTICS

- Evening administration of **ranitidine** is justified from the point of view of chronopharmacology.



CHRONOTHERAPEUTICS

- Chronotherapy found use in:

  oncology, asthma therapy, hypertension, CAD, strokes, sleep apnea, GI tract disorders, vocational medicine, allergies, immunologic disorders.

CHRONOTHERAPEUTICS

- The same medication when dosed in the evening rather than morning need not have the same pharmacokinetics or efficiency of effect. Moreover, different formulations of the same therapeutic agent may vary greatly in the extent to which their pharmacokinetics are administration time-dependent because of proprietary disparities in the respective drug-delivery systems. In the past, the effects of the body's rhythms on the behavior of medications were not well understood by the medical community; thus they were not taken into account in the design and interpretation of prevention trials.

CHRONOTHERAPEUTICS

- Due to advances in chronobiology, chronopharmacology, and global market constraints, the traditional goal of pharmaceutics (e.g. design drug delivery systems with a constant drug release rate) is becoming obsolete. However, the major bottleneck in the development of drug delivery systems that match the circadian rhythm (chronopharmaceutical drug delivery systems: ChrDDS) may be the availability of appropriate technology. The last decade has witnessed the emergence of ChrDDS against several diseases. The increasing research interest surrounding ChrDDS may lead to the creation of a new sub-discipline in pharmaceutics known as chronopharmaceutics. This review introduces the concept of chronopharmaceutics, addresses theoretical/formal approaches to this sub-discipline, underscores potential disease-targets, revisits existing technologies and examples of ChrDDS. Future development in chronopharmaceutics may be made at the interface of other emerging disciplines such as system biology and nanomedicine. Such novel and more biological approaches to drug delivery may lead to safer and more efficient disease therapy in the future.